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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,711	03/18/2004	John G. Keimel	P0011802.00	7831

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Hahn & Voight-Medtronic, Inc. patent applications
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EXAMINER	
WILSON, LARRY ROSS	

ART UNIT	PAPER NUMBER
3767	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,711	KEIMEL ET AL.	
	Examiner	Art Unit	
	LARRY R. WILSON	3767	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12,14,16-21,23-26,28-34,44-49,51,52,54-60,62,63,65,66 and 68-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-7, 9-10, 12, 14, 16-21, 23-26, 28-34, 44-49, 51-52, 54-60, 62, 63, 65, 66, and 68-75.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-6, 9, 10, 12, 14, 18-21, 23-26, 28-33, 45-49, 51-52, 54-59, 62, 63, 65, 66, 69-75, are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,814,014 to Dennis D. Elsberry et al. (Elsberry) in view of U.S. Patent 5,433,946 to Howard J. Allen, Jr. et al. (Allen) in view of U.S. Patent Application 2003/0129186 to Richard Beliveau et al (Beliveau).

In regards to claim 1, Elsberry teaches a system comprising an implantable catheter system (Fig. 1, #22), and a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36), and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a therapeutic protein formulation that has been modified for enhanced cellular uptake properties, wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid, said

modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein.

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

In regards to claim 28, Elsberry teaches a system comprising a means of physically bypassing the blood-brain barrier, via an implantable catheter system (Fig. 1,

#22), and a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36) and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a means for providing a therapeutic protein formulation that has been modified for enhanced cellular uptake properties, wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein.

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

In regards to claim 54, Elsberry teaches a system comprising an implantable catheter system (Fig. 1, #22) to physically deliver said therapeutic protein formulation across the blood-brain barrier at a programmed delivery rate (col. 4, lines 32-36) for the purpose of treating patients diagnosed with at least one neurological disease of the central nervous system (abstract), a pump (Fig. 1, #10) that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region (col. 3, lines 19-20), wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation (col. 4, lines 32-36), and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease (col. 3, line 66-col. 4, line 3 – shows the sensing of hyperexcitation indicative of

neurological disease), genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof.

But Elsberry does not teach a therapeutic protein formulation, wherein at least some proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein.

Allen teaches a therapeutic protein formulation that has been modified for enhanced cellular uptake properties (col. 3, lines 45-51, col. 4, line 46-47), wherein at least some of the proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins (Allen col. 4, lines 44-47), said modified proteins have been modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein (col. 4, lines 44-47).

Neither Elsberry nor Allen teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid; said linker is a streptavidin-biotin complex.

Beliveau teaches the conjugation comprises a linker species existing between said therapeutic protein and said transport aid (para. 26); said linker is a streptavidin-biotin complex (para. 189).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the therapeutic protein formulation of Allen, and the linker

species of Beliveau in the system of Elsberry, in order to in order to reduce therapeutic protein loss to clearance and inactivation (col. 1, lines 48-51, 62-64) as taught by Allen, and to modulate blood-brain barrier transport (abstract) as taught by Beliveau.

In regards to claims 2-6, 9, 10, 12, 14, 18-21, 23-26, 29-33, 45-49, 51-52, 55-59, 62, 63, 65, 66, 69-75, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, and further teaches:

Claims 2, 29, 55: the neurological diseases treated are selected from the group consisting of lysosomal storage diseases, protein deficiency diseases, enzyme deficiency diseases, inborn errors of metabolism, neurodegenerative diseases (col. 2, lines 19-21), and combinations thereof;

Claims 3, 30, 56: said neurological diseases are inborn errors of metabolism selected from the group consisting of … mucopolysaccharidosis (Allen Table 1, line 32);

Claims 4, 31, 57: said neurological diseases are selected from the group consisting of Fragile X Syndrome, Parkinson's disease (Elsberry col. 2, line 20), Alzheimer's disease, and combinations thereof;

Claims 5, 32, 58: the therapeutic protein formulation comprises enzymes providing for enzyme replacement therapy (Allen col. 1, lines 38-42);

Claims 6, 33, 59: the enzymes are selected from the group consisting of … alpha-L-iduronidase (Allen Table 1, line 32);

Claims 9, 62: said modified proteins have been modified by incorporating into their structure amino acid sequences providing for an intrinsic transport aid (col. 4, lines 44-47);

Claims 10, 63: said modified proteins are fusion proteins (col. 4, lines 44-47 – by conjugating one is also fusing two proteins together into one peptide);

Claims 12, 65: the transport aid comprises at least a portion of a species selected from the group consisting of recombinant human melanotransferrin, p97, tetanus toxin fragment C, endogenous lectins (Allen col. 4, lines 61-64), biotin, and combinations thereof;

Claims 14, 66: said linker is selected from the group consisting of peptide linkages, disulfide linkages, and combinations thereof (Beliveau para. 26);

Claims 18, 45, 69: implantable catheter system is implanted so as to deliver said therapeutic protein formulation to regions selected from the group consisting of... intracerebroventricular (Elsberry col. 2, lines 29-32);

Claims 19, 70: further comprising an inlet (Fig. 12, #14);

Claims 20, 48, 71: further comprising a reservoir (Elsberry col. 3, lines 17-20);

Claims 21, 49, 72: said reservoir is implantable and refillable (col. 3, lines 15-20);

Claims 23, 51, 73: the pump comprises an integrated reservoir (col. 3, lines 15-20 – implies an integrated reservoir for the inlet 14 to connect to something);

Claims 24, 52, 74: said pump is implantable (Elsberry col. 2, lines 19-22);

Claim 25, 46, 75: the implantable catheter system comprises at least one branched catheter permitting delivery to at least two separate regions using one primary catheter line (Elsberry col. 3, lines 47-51);

Claim 26, 47: the branched catheter is bifurcated (col. 3, line 47 – "divided into twin tubes" implies a bifurcation).

3. Claims 7, 16, 17, 34, 44, 60, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsberry, as modified by Allen and Beliveau, as applied to claims 1, 28, and 54 above, and further in view of U.S. Patent 6,015,572 to Leu-Fen H. Lin et al. (Lin).

In regards to claims 7, 34, and 60, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, but does not teach the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF, FMRP, and combinations thereof.

Lin teaches the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF (col. 1, lines 25-27), FMRP, and combinations thereof.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the GDNF proteins of Lin in the system of Elsberry, as modified by Allen, in order to treat nerve damage and related diseases (col. 1, lines 25-27) as taught by Lin.

In regards to claims 16, 17, 44, and 68, Elsberry, as modified by Allen and Beliveau, teaches the system of claims 1, 28, and 54, but does not teach said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation; the integrity and activity of the protein formulation is achieved by the addition to said therapeutic protein formulation, at least one species operable for maintaining a desired pH.

Lin teaches said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation; the integrity and activity of the protein

formulation is achieved by the addition to said therapeutic protein formulation, at least one species operable for maintaining a desired pH (col. 19, lines 50-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further included the pH maintaining excipients of Lin in the system of Elsberry, as modified by Allen, in order to provide a "physiologically-compatible, slow-release formulation" (col. 19, lines 50-52) as taught by Lin.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 2, 4, 28, 29, 31, 54, 55, and 57 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,814,014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim requires the structural features of the instant application which are a pump, a catheter capable of delivering a therapeutic dosage, a sensor for generating a signal

related to an attribute of the nervous system, and control means responsive to signal generated. One of ordinary skill would have found it obvious to substitute drugs for protein formulations and proteins are known to influence the excitation response of neurons, e.g. glutamate.

6. Claims 1, 2, 4, 24, 28, 29, 31, 52, 54, 55, 57, and 74 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, and 11 of U.S. Patent No. 6,056,725. Although the conflicting claims are not identical, they are not patentably distinct from each other because similar structure is recited for treating Alzheimer's, a pump, a source of indomethacin, a catheter connected to the pump into the hippocampus or lateral ventricle, and the pump adapted for subcutaneous placement. The present invention does not require the adjustable catheter, it requires a catheter, thus one of ordinary skill would have found it obvious to make the catheter adjustable in order to provide treatment to a larger population of patients, and one of ordinary skill would have found it obvious to substitute indomethacin for a therapeutic protein.

Response to Amendment

7. The amendment to claims 1, 9, 12, 14, 23, 24, 28, 51, 52, 54-55, 62, 65, and 66 in the response filed on 26 February 2010 are acknowledged.

8. The cancellation of claims 8, 11, 13, 15, 61, 64, and 67 in the response filed on 26 February 2010 is acknowledged.

9. The amendment to claims 23, 24, 51, 52, and 54 are sufficient to overcome the objections to the claims, which are withdrawn.

Response to Arguments

10. Applicant's arguments filed 26 February 2010 have been fully considered but they are not persuasive.

11. Applicant's argument that Beliveau does not teach a streptavidin-biotin complex as a linker between a therapeutic protein and a transport aid is not persuasive, because Beliveau teaches a linker between for protein conjugation (para. 26). Later, Beliveau teaches specifically a streptavidin-biotin complex used for linking a label to a protein, however one of ordinary skill would have found it obvious to substitute a transport aid, or any other desired peptide portion for the label, while still maintaining the streptavidin-biotin linking complex. Additionally, such a substitution would not render Elsberry or Allen unsuitable for the intended purpose, because complexing two proteins for additional functionality is well known, as taught by Allen (col. 4, lines 44-60) and Beliveau (para. 26).

12. Applicant's arguments that the lack of a streptavidin-biotin complex as a linker in the double patenting rejection to U.S. Patent 5,814,014 and U.S. Patent 6,056,725 are not persuasive, because substituting the drug for protein, modified with a streptavidin-biotin complex or not, would be obvious to one of ordinary skill in the art.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY R. WILSON whose telephone number is (571)270-5899. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM (EST).

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kevin C. Sirmons can be reached on 571-272-4965. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

16. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LARRY R WILSON/
Examiner, Art Unit 3767
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